Claim 14 has been amended as indicated above. Support for this amendment is found in the specification at, for example, page 3, lines 13-19, page 3, line 34, in Examples 3 and 4, and in original claim 14. *In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Claims 19-21 are presented, which are directed to a method of binding a powder or granule composition, a method of making a compressed tablet with improved color stability and tablet hardness, and a method of binding L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, respectively. Support for claims 19-21 is found in the specification at, for example, page 3, lines 13-19, page 3, line 34, and in Examples 3 and 4.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

**Claim of Benefit to Priority Applications**

In the Office Action, the Examiner acknowledged the applicant's claim of priority based on EP 99125639.7, filed December 22, 1999. The Examiner asserted, however, that the Applicant has not filed a certified copy of the priority document. (Paper 3 at 2). This statement is in error.

A certified copy of the priority document was filed with the application on December 15, 2000. Attached as Exhibit 2, is a copy of the date-stamped postcard that accompanied the application. As the Examiner will note, item 6 on the postcard clearly identifies the certified copy of the EP priority document. (For the Examiner's convenience a copy of the priority document is attached as Exhibit 3.) As is well settled, "a postcard receipt which itemizes and properly identifies the items which are being filed serves as *prima facie* evidence of receipt

in the PTO of all the items listed thereon on the date stamped thereon by the PTO." See MPEP § 503. Thus, there can be no doubt that the priority document was filed, and that it was received by the PTO. In view of the foregoing, acknowledgment of the receipt of the certified copy of the priority document EP 99125639.7 and that the claim benefit has been perfected is respectfully requested.

**Obviousness Rejection**

Claims 1-18 were rejected solely under 35 USC §103(a) as being unpatentable over Schmidt, *et al.*, U.S. Patent No. 4,605,666 ("Schmidt"). (Paper No. 3 at 3).

For the reasons set forth below the rejection, respectfully is traversed.

Schmidt discloses a process for preparing a powder containing a water-soluble vitamin by ***spray drying an aqueous slurry of the vitamin and a binder***, a lubricant, and optionally an adsorbent and an additional excipient. (Col. 1, line 52 - Col. 2, line 54).

In making the rejection, the Examiner asserted that Schmidt discloses "a powder composition prepared by spray drying comprising an aqueous slurry of a water-soluble vitamin (i.e. sodium ascorbate, ascorbic acid, calcium ascorbate, etc...); a binder (*i.e.*, microcyrstalline cellulose, etc ...); a lubricant (*i.e.*, stearic acid, magnesium stearate, calcium stearate, etc...); and an excipient (i.e. pectin, starch, etc...)." (Paper No. 3 at 3). The Examiner acknowledged, however, that "the reference fails to teach the specific utility of pectin in combination of sodium ascorbate or ascorbic acid to stabilize color of claimed invention...," and that "Schimdt *et al.* differs from the claimed invention in the specific utility of pectin in claimed composition; and the use of citrus pectin." (*Id.* at 4.)

To fill the acknowledged gap, the Examiner relied on Newlin *et al.* as "teaching" the use of pectin as an anti-browning agent in a peanut butter composition. (*Id.*).

The Examiner then concluded that "it would have been obvious to a person skilled in the art to formulate the composition containing L-ascorbic acid and/or its salts in combination with pectin...." (*Id.*). The Examiner further asserted that "[o]ne having ordinary skill in the art would have [been] motivated to use well known anti-browning agent or color improving agent such as pectin ...." (*Id.*).

Initially, we note that Newlin has not been made of record, has not been furnished by the Examiner, and is not properly cited. Accordingly, the Examiner is requested to correct this error and forward a correct copy of the reference as required by MPEP 707.05(g).

The improper citation of Newlin renders the rejection unclear and incomplete. Further, the inability of the applicant to review Newlin makes it impossible to meaningfully respond to the rejection. Accordingly, the rejection falls far short of providing applicants with the notice required by 35 USC § 132. See also MPEP § 707.07(d) (the Examiner must "fully and clearly" state the grounds for any rejection). For this reason alone, the rejection is insufficient as a matter law, and should be withdrawn.

Notwithstanding the legally insufficient nature of the rejection, we address its merits, in so far as they are understood, below. Assuming, Schimdt and the phantom Newlin document are even combinable, which is not admitted, the rejection fails to identify where in Schmidt or Newlin there is disclosed or suggested spraying pectin onto fluidized particles of L-ascorbic acid as presently recited in claims 14-21. It is respectfully submitted that spray drying the entire composition, as disclosed by Schmidt (See Col. 1, line 52 - Col. 2, line 54), is fundamentally different than spraying a pectin binder onto fluidized particles of L-ascorbic acid

as recited in, *e.g.*, claims 14-21. And, the rejection provides no evidence or reasoning why the presently claimed processes would be suggested by Schmidt or Newlin, alone or in combination. Thus, the rejection of claims 14-21 is insufficient as a matter of fact and law and should be withdrawn.

Furthermore, the composition/tablet claims, *i.e.* claims 1-13 are made by the unique processes recited in claims 14-21. Given the unique processing steps recited in claims 14-21, especially the spraying of the pectin binder onto the fluidized L-ascorbic acid particles, the rejection provides no evidence or reasoning why the compositions disclosed by Schmidt would suggest the compositions and tablets recited in claims 1-13. Thus, the rejection of claims 1-13 is insufficient as a matter of fact and law and should be withdrawn.

Accordingly, for the reasons set forth above, acknowledgment of the receipt of the certified copy of the priority document and the perfection of our claim to benefit, entry of the amendments, withdrawal of the rejection, and allowance of the claims is respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231, on December 4, 2001.

Stephen J. Brown, Reg. No. 43,519

Respectfully submitted,

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## "Marked Up" Amendments to Claims Pursuant to Rule 1.121(c)

1. (Amended) A powder or granule composition comprising:

(a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, and

(b) about 0.1 to about 10% by weight of pectin binder, calculated based on the total weight of the composition thereof.

8. (Amended) A compressed tablet formed from a powder or granule composition comprising:

(a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, and

(b) about 0.1 to about 10% by weight of pectin binder, based on the total weight of the composition.

14. (Amended) A process for preparing a powder or granule composition comprising:

(a) forming a fluidized bed comprising fluidized particles of [preparing an aqueous slurry comprising] L-ascorbic acid and/or a pharmaceutically acceptable salt thereof [and about 0.1% to about 10% by weight of pectin]; and

(b) spraying from about 0.1 % to about 10% by weight of a pectin binder onto the fluidized particles of L-ascorbic acid [spray drying the slurry to form the powder or granule].

December 15, 2000 Docket No. 20529/111697

In re Patent Application of:
Chyi-Cheng CHEN *et al.*
Serial No.: Unassigned
Filed: Herewith
For: **L-ASCORBIC ACID AND PECTIN COMPOSITION**

Enclosed:

1. Certificate of Express Mailing (1 p)
2. Transmittal Letter (3 pp) in duplicate
3. Specification, Claims and Abstract (12 pp)
4. Declaration and Power of Attorney (3 pp) (executed)
5. Two (2) Assignments and Recordation Cover Sheets (4 pp)
6. Certified Priority Document EP 99125639.7
7. Check for $790.00 (Filing fee)
8. Two (2) Checks for $40.00 each (Assignment fee)
9. Return Postcard



**EXPRESS MAIL NO. EL470275878US**

**PLEASE DATE STAMP AND RETURN TO ACKNOWLEDGE RECEIPT**

KCH:sc C38435/111697

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|---|---|---|

# Bescheinigung Certificate Attestation

| | | |
|---|---|---|
| Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein. | The attached documents are exact copies of the European patent application described on the following page, as originally filed. | Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante. |

| Patentanmeldung Nr. | Patent application No. | Demande de brevet n° |
|---|---|---|
| | 99125639.7 | |

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 26/10/00
LA HAYE, LE

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# Blatt 2 der Bescheinigung
# Sheet 2 of the certificate
# Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 99125639.7
Demande n°:

Anmeldetag:
Date of filing: 22/12/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
F. HOFFMANN-LA ROCHE AG
4070 Basel
SWITZERLAND

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Composition comprising L-ascorbic acid and pectin

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

| Staat: State: Pays: | Tag: Date: Date: | Aktenzeichen: File no. Numéro de dépôt: |
|---|---|---|

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
/

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du depôt:

Bemerkungen:
Remarks:
Remarques:

F. HOFFMANN-LA ROCHE AG, CH-4070 Basel

CASE 20529

# Composition comprising L-ascorbic acid and Pectin

The present invention refers to a composition in the form of a powder and/or granules, which contain as principal components L-ascorbic acid and/or a pharmaceutically acceptable salt thereof together with pectin. The composition according to the present invention is directly compressible into tablets with good taste, sufficient mechanical strength and hardness, with excellent color stability as well as sugar-free and starch-free. The addition of adjuvants and excipients to the composition for producing tablets is optional.

Different methods have been suggested for producing L-ascorbic acid powder or granules which are directly compressible into tablets. Hydroxypropylmethylcellulose (HPMC) and starch are today considered as the standard binders for producing such powders and granules. For sugar-free and starch-free tablets, the powder or granules is generally produced with HPMC as binder, although the color stability of such powders or granules, and tablets obtained therefrom, is not sufficient.

It was now found that a composition containing L-ascorbic acid and/or its salts together with pectin, may be obtained in the form of a powder or of granules with greatly improved color stability. Tablets made from such compositions have good taste, mechanical strength, and/or hardness, and in addition surprisingly have greatly improved color stability. In such a composition the pectin preferably is present in a quantity with in the range of about 0.1 to about 10% by weight, calculated to the total weight of the composition thereof.

The present invention is defined in the claims.

The present invention specifically refers to a composition in the form of a powder or granules comprising:

(a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,

(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated to the total weight of the composition thereof, and

(c) optionally adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated to the total weight of the composition.

The present invention further refers to methods of producing the composition of the present invention. The present invention further refers to tablets obtained from the composition of the present invention.

L-ascorbic acid is known *per se*. Numerous pharmaceutically acceptable salts thereof are known. Preferred from these is sodium ascorbate.

Pectin is known *per se*. Pectin is a polysaccharide and described for example in the book entitled Industrial Gums, third edition, Academic Press, Inc., 1993, pages 257ff. Commercial pectins are generally produced from either citrus peel or apple pomace. Other possible sources are sugarbeet, sunflower and mango. Preferred pectins to be used within the scope of the present invention are citrus pectins, which generally have lighter color than apple pectins and, thus, do not impart significant color to the granule product.

Pectin is preferably used in quantities within the range of about 0.1% to about 10% by weight, preferably in quantities of about 0.5% to about 5% by weight and most preferably in quantities of about 0.5% to about 2% by weight, calculated to the total weight of the composition thereof. Experiments have shown that a composition consisting of 95-99% by weight of L-ascorbic acid and/or the pharmaceutically acceptable salt thereof and 5-1% by weight of pectin, the two components totalling 100% by weight, i.e. with no other components present, yield tablets of very good quality and excellent color stability.

Adjuvants may optionally be added. Suitable adjuvants are for example starch, HPMC, polyols. Preferably no adjuvants are added.

The composition of this invention may be produced by any method known *per se* for the production of powders or granules. Preferred are fluidized-bed granulation, high-shear granulation, extrusion, spray-drying and wet granulation.

For obtaining the composition of the present invention by spray-drying it is convenient to prepare an aqueous slurry of all the components. The slurry has preferably a solid content of about 10 to 70% by weight, and preferably about 25 to 50% by weight. The slurry is then spray-dried in a manner known per se.

For obtaining the composition of the present invention by fluidized-bed granulation it is convenient to use a known fluidized-bed granulating apparatus which comprises a fluidized-bed drying device fitted with spray means. Preferably the L-ascorbic acid and/or a pharmaceutically acceptable salt thereof form the fluidized bed, which is fluidized by air. The pectin, as well as optional adjuvants, dissolved in an appropriate amount of water and sprayed in the form of an atomized mist onto the fluidized particles in such a manner that the granulating and drying operations is accomplished in a single step. The granulating process is continued until the required amount of the pectin binder has been deposited onto the fluidized particles and an appropriate granule size distribution is obtained. The granules are sieved to remove the fractions of granules which are either too large or too small.

The composition thus obtained may be compressed into tablets with conventional tabletting methods and machinery. Optionally the powder or the granules may further be mixed with a lubricant or a mixture of lubricants and then compressed into tablets. If additional lubricant is used it is preferably selected from the group of stearic acid or the magnesium or calcium salt thereof, or glyceryl behenate 45 (Compritol 888 ATO), preferably in an amount of about 0.5 to 4% by weight, calculated to the total weight of the composition. Or the composition may be mixed with excipients. Examples for excipients are dextrinized sucrose (Di Pac sugar), micro-crystalline cellulose or starch. The amount of the excipients depends on the dose level of vitamin C and the tablet size. It is used in the level of a tablet weight minus vitamin C and lubricant.

A single tablet as obtained according to the present invention contains preferably 50 mg to 1500 mg, preferably 500 mg to 1000 mg of L-ascorbic acid and/or the pharmaceutically acceptable salt thereof, corresponding to an appropriate daily doses of vitamin C. The following examples illustrate the invention.

Example 1

L-ascorbic acid crystals (2475 g, Roche Ascorbic Acid Fine Granular, F. Hoffmann - La Roche AG.), was placed in a stainless container of a wet granulator (Ultra Power model from KitchenAid, Michigan, USA). Pectin (27.36 g, Pectin USP, Danisco Ingredients, Denmark) was dissolved in distilled water (350 g). The pectin solution (151.3 g) was added to the ascorbic acid crystals over a period of 10 minutes with mixing. After the addition of pectin solution, the paste was mixed for another 10 minutes and then pressed through a screen with 2mm–openings to form a noodle-like particles, which was dried in trays in a 45°C / 25% relative humidity (RH) room for 4 hours. The dry particles were milled and sieved to give the particle size distribution as shown in Table 1A.

Table 1A

| Particle size, micron | % |
|---|---|
| > 710 | 0.7 |
| > 500 | 16.2 |
| > 355 | 29.8 |
| > 250 | 19.9 |
| > 125 | 21.9 |
| < 125 | 11.4 |
| Total | 100 |

The granules were mixed with other excipients as shown in the following Table 1B and compressed at 20 KN to give 786 mg tablets. The hardness of the tablet was 88N.

Table 1B

| | Parts by weight |
|---|---|
| Granule Sample | 108.64 |
| Roche Ascorbic Acid 90% Granulation | 79.66 |
| White Di Pac sugar | 301.27 |
| Compritol 888 ATO | 10.43 |

To evaluate the color stability, the granules were dried at 45 °C to about 0.08% moisture content, sealed in aluminum bags and stored at ambient temperature. The Whiteness Index (CIE) of the granules was determined at various time intervals using a Hunterlab Ultrascan B256 (Hunter Associates Laboratory, Inc.Reston, VA. USA). For comparison, the reduction in whiteness index was obtained by subtracting the whiteness indices determined at various storage times from the initial whiteness index. Granules with poor color stability show high whiteness index reduction.

Color Stability: Whiteness Index reduction: 1.07 (after 1 month), 2.70 (after 2 months)

Example 2

Example 1 was repeated with the exception that Hydroxypropylmethyl-cellulose (HPMC)(Methocel E15LV, The Dow Chemical Co., Michigan, USA) was used in place of pectin. The granule particle size distribution was as given in Table 2.

Table 2

| Particle size, micron | % |
|---|---|
| > 710 | 0.3 |
| > 500 | 14.4 |
| > 355 | 35.0 |
| > 250 | 23.2 |
| > 125 | 19.8 |
| < 125 | 7.4 |
| Total | 100 |

Compressed at 20 KN compression force, the hardness of the tablet was 75 N.

The color stability was determined according to Example 1. Color Stability: Whiteness Index reduction: 8.49 (after 1 month temperature), 27.1 (after 2 months).

Comparing Example 1 with Example 2, it is obvious that granules or powder made with pectin as binder is far superior to that made with HPMC with regard to tabletting compressibility and color stability.

Example 3

Sodium L-ascorbate (F. Hoffmann - La Roche AG, Switzerland, particle size etc) was used. A pectin solution was prepared by dissolving 27.3 g of pectin (Pectin USP, 8.4% moisture content, Danisco Ingredients, Denmark) in 1000 g of water. Sodium ascorbate powder was placed in a Glatt Fluidized-Bed granulator (Model Uniglatt, Switzerland) and sprayed with a fine mist of pectin solution. The granulation conditions were as follows:

L-Sodium ascorbate: 594 g

Pectin solution: 246.6 g

Pectin solution spraying rate: 6.7 g/minute

Inlet Air temperature: 80 °C

a) The granules leaving the apparatus had a moisture content of 0.19% by weight, calculated to the granule weight. The granule particles were sieved to give the particle size distribution as shown in Table 3A

Table 3A

| Particle size, micron | % |
|---|---|
| > 710 | 12.16 |
| > 500 | 18.03 |
| > 355 | 22.90 |
| > 250 | 16.42 |
| > 125 | 16.82 |
| < 125 | 13.67 |
| Total | 100 |

b) The granules (125-750 micron fraction) as obtained above in Example 3 were mixed with the excipients as shown in the following Table 3B and compressed into tablets of 767 mg weight.

Table 3B

| | Parts |
|---|---|
| Sample | 108.64 |
| Roche Ascorbic Acid 90% Granulation | 79.66 |
| White Di Pac sugar | 301.27 |
| Compritol 888 ATO | 10.43 |

The tablet hardness at various compression forces is as follows:

Hardness (Compression Force): 118 N (5 KN), 145 N (10 KN), 174 N (15 KN), 203 N (20 KN), 224 N (25 KN), 246 N (30 KN)

Example 4

Example 3 was repeated with the exception that Hydroxypropylmethyl-cellulose (HPMC)(Pharmacoat, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) was used in place of pectin.

The granulation conditions were as follows:

L-Sodium ascorbate: 594 g

HPMC solution: 246.6 g

Pectin solution spraying rate: 6.7 g/minute

Inlet Air temperature: 80 °C

The granule particles were sieved to give the particle size distribution as shown in Table 4

Table 4

| Particle size, micron | % |
|---|---|
| > 710 | 0.2 |
| > 500 | 1.5 |
| > 355 | 5.2 |
| > 250 | 17.5 |
| > 125 | 58.9 |
| < 125 | 11.1 |
| Total | 100 |

The granules (125-750 micron fraction) were mixed with the excipients-and compressed into tablets of 767 mg weight.

The tablet hardness at various compression forces is as follows:
Hardness (Compression Force): 95 N (5 KN), 132 N (10 KN), 151 N (15 KN), 179 N (20 KN), 177 N (25 KN), 200 N (30 KN).

Comparing Example 3 with Example 4, again, granules or powder made with pectin as binder is far superior to that made with HPMC with regard to tabletting compressibility.

Claims

1. Composition in the form of a powder or granules comprising:
(a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated to the total weight of the composition thereof, and
(c) optionally adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated to the total weight of the composition.

2. Composition according to claim 1, wherein the pharmaceutically acceptable salt of L-ascorbic acid is sodium ascorbate.

3. Composition according to claims 1 or 2, wherein the pectin has been produced from citrus peel, apple pomace, sugarbeet, sunflower and/or mango and preferably is a citrus pectin.

4. Composition according to any one of the claims 1-3, wherein the pectin is present in quantities within the range of about 0.5% to about 5% by weight, calculated to the total weight of the composition thereof.

5. Composition according to any one of the claims 1-3, wherein the pectin is present in quantities within about 0.5% to about 2% by weight, calculated to the total weight of the composition thereof.

6. Composition according to any one of the claims 1-5, wherein said composition consists of 95-99% by weight of L-ascorbic acid and/or a pharmaceutically acceptable salt thereof and 5-1% by weight of pectin, the two components totalling 100% by weight.

7. Composition according to any one of the claims 1-6, wherein said composition contains added adjuvants, preferably starch, HPMC and/or polyols.

8. Composition according to any one of the claims 1-7, which has been produced by fluidized-bed granulation, high-shear granulation, extrusion, spray-drying or wet granulation.

9. Method for obtaining the composition according to any one of the claims 1-8, comprising preparing an aqueous slurry of all the components, preferably having a solid content of about 10 to 70% by weight, and preferably about 25 to 50% by weight and spray-drying the slurry in a manner known per se.

10. Method for obtaining the composition according to any one of the claims 1-8, comprising forming a fluidized bed with L-ascorbic acid and/or a pharmaceutically acceptable salt thereof within a fluidized-bed drying device fitted with spray means, said fluidized bed being fluidized by air, and spraying pectin as well as optional adjuvants which are dissolved in an appropriate amount of water in the form of an atomized mist onto the fluidized particles until the required amount of the pectin binder has been deposited onto the fluidized particles and an appropriate granule size distribution is obtained.

11. Composition according to any one of the claims 1-8, in the form of a compressed tablet.

12. Composition according to claim 11, containing a lubricant or a mixture of lubricants, preferably selected from the group of stearic acid or the magnesium or calcium salt thereof, or glyceryl behenate 45 (Compritol 888 ATO), preferably in an amount of about 0.5 to 4% by weight, calculated to the total weight of the composition.

13. Composition according to claims 11 or 12, containing excipients, preferably selected from dextrinized sucrose (Di Pac sugar), microcrystalline cellulose or starch.

14. Composition according to any one of these claims 10-13, wherein a single tablet contains 50 mg to 1500 mg, preferably 500 mg to 1000 mg of L-ascorbic acid and/or the pharmaceutically acceptable salt thereof.

## Abstracts

Composition in the form of a powder or granules comprising (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, (b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated to the total weight of the composition thereof, and (c) optionally adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated to the total weight of the composition.

Hu16.12.99